Patent
Attorney's Docket No.1034123-000122

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of)	**MAIL STOP Amendment**
)	
David Feifel)	Group Art Unit: 1649
)	
Application No.: 10/538,245)	Examiner: Aditi DUTT
)	
Filed: June 7, 2005)	Confirmation No.: 3580

For: METHOD OF INHIBITING NEURAL
TRANSMISSION MEDIATED BY
SEROTONIN-2A AND ENHANCING
SENSORIMOTOR GATING

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DECLARATION UNDER 37 C.F.R. § 1.131

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

1.   I, David Feifel, having an address at 8241 La Jolla Scenic Drive North, La Jolla, California, 92037 am the inventor of the above-captioned United States Patent Application Serial No.10/538,245, which claims priority to International Patent Application Serial No. PCT/US03/039196, filed December 8, 2003 and United States Provisional Patent Application No. 60/431,937, filed December 9, 2002.

2.   I am familiar with the prosecution history of Patent Application Serial No. 10/538,245. I understand that Hedley et al. is being cited as a reference against the claims of the application because Hedley et al. allegedly teaches the claimed invention prior to my invention date.

3.   I submit that Hedley, et al. (Society for Neuroscience, 2002, Online) is not available as prior art under 35 U.S.C §102 or §103, because the publication is not prior to my invention date.

4.   I submit that I conceived of the use of NT69L as a modulator of schizophrenia and other neuropsychiatric problems prior to Hedley et al. (published August 2002) and that I was diligent in reducing the claimed invention to practice up to and including the filing date of U.S. Patent Application No. 60/431,937, filed on December 9, 2002.

5.   Evidence of the conception of the claimed invention is supplied in the form of a copy of notes (Exhibit A) from my laboratory notebooks, prior to August 2002, the publication date of Hedley et al. These notes show the reduction to practice of NT69L in the rat model of schizophrenia (the same model used by Hedley et al. in the publication being cited after my invention date).

Prior to the public availability of Hedley et al. (August 2002), the testing and identification of NT69L as a potential modulator of schizophrenia, bipolar disorders, anxiety and depression in rat models was first performed by me or under my direction at the University of California, San Diego, using an accepted rat model having reduced prepulse inhibition. I, or my technicians at my direction, first tested NT69L in the rat pre-pulse inhibition model startle reflex assay as early, and earlier than, July 2002, prior to Hedley et al.'s publication.

The laboratory pages of Exhibit A show dose calculations for NT69L and Rat Startle Run Sheets generated prior to August 2002. The Rat Startle Run Sheets demonstrate measurements of control and test groups in the prepulse inhibition (PPI) of the acoustic startle response rat model, one of the models used in Hedley et al. These experiments were carried out prior to August 2002.
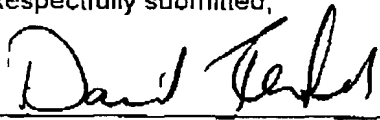
I was diligent from the time of conception of the invention with respect to the use of neurotensin agonists including NT69L in the treatment of various psychotic disorders including bipolar, anxiety, depression and schizophrenia prior to August 2002 until the filing of the priority application on December 9, 2002.

6.   I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful

false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Respectfully submitted,

Date January 02 08

David Feifel

Rat Startle Run Sheet
NT69 / DOI

Experiment #: DF92D1
Date: ▮▮▮▮▮▮
Session: EISOCRIT/LOCOMOTOR (DF92D1)
Run By: KP

Comments:
Protocol # 5-062-06
Runs # 1-6 up @ 7:30am
Runs # 7+8 up @ 8:33am

Groups:	NT69	DOI
(white)	1 = saline	1 = saline (white)
(yellow)	2 = 0.01 mg/kg	2 = 0.5 mg/kg bl.
(orange)	3 = 0.1 mg/kg	
(red)	4 = 1.0 mg/kg	

Comments	LOCO cge #	Box	Rat #	Group	Weight	(20min) LOCO	INJ NT (30)	(30min) LOCO	SC inj DOI	(20min) LOCO	(20min) PPI	(20min) LOCO	File Name	
	1	1	10	1 1	298	8:00	8:20	8:22	8:52	8:54	9:15	9:36	df92d1r1	✓
	2	2	12	2 2	278	(1-10)		(12-26)		(28-37)		(49-58)		
	3	3	2	3 1	330	↓		↓		↓	↓	↓		
	4	4	5	4 2	284	8:20	↓	8:52	↓	9:14	9:35	9:56		
	5	1	3	1 2	302	8:26	8:46	8:48	9:18	9:20	9:41	10:02	df92d1r2	✓
	6	2	8	2 1	269	(14-23)		(25-31)		(41-50)		(62-71)		
	7	3	7	3 2	297	↓		↓		↓	↓	↓		
	8	4	1	4 1	290	8:46	↓	9:18	↓	9:40	10:01	10:22		
	9	1	6	4 2	281	8:52	9:12	9:14	9:44	9:46	10:07	10:28	df92d1r3	✓
	10	2	18	1 1	299	(27-36)		(38-52)		(54-63)		(75-84)		
	11	3	13	2 2	288	↓		↓		↓	↓	↓		
	12	4	4	3 1	302	9:12	↓	9:44	↓	10:06	10:27	10:48		
	1	1	21	4 1	309	10:00	10:20	10:22	10:52	10:54	11:15	11:36	df92d1r4	✓
	2	2	14	1 2	297	(61-70)		(72-82)		(88-97)		(109-118)		
	3	3	17	2 1	297	↓		↓		↓	↓	↓		--
	4	4	9	3 2	281	10:20	↓	10:52	↓	11:14	11:35	11:56		
	5	1	25	3 1	287	10:26	10:46	10:48	11:18	11:20	11:41	12:02	df92d1r5	✓
	6	2	29	4 2	304	(74-83)		(85-99)		(101-110)		(122-131)		
	7	3	23	1 1	297	↓		↓		↓	↓	↓		
	8	4	22	2 2	288	10:46	↓	11:18	↓	11:40	12:01	12:22		
	9	1	16	3 2	295	10:52	11:12	11:14	11:44	11:46	12:07	12:28	df92d1r6	✓
	10	2	24	4 1	290	(87-96)		(98-112)		(114-123)		(135-144)		
	11	3	27	1 2	287	↓		↓		↓	↓	↓		
	12	4	19	2 1	309	11:12	↓	11:44	↓	12:06	12:27	12:48		
	1	1	35	2 2	289	12:00	12:20	12:22	12:52	12:54	1:15	1:36	df92d1r7	✓
	2	2	31	3 1	255	(121-130)		(133-146)		(148-157)		(168-177)		

Experiment #: DF92D1
Date: ▓▓▓▓▓▓
Session: EISOCRIT/LOCOMOTOR
Run By: KP

Comments:
Protocol # 5-062-06

Rat Startle Run Sheet
NT69 / DOI

Groups:	NT69	DOI
1	1=saline	1=saline
2	2=0.01 mg/kg	2=0.5 mg/kg
3	3=0.1 mg/kg	
4	4=1.0 mg/kg	

Comments	loco cage#	Box	Rat#	Group	Weight	Time 1 (90min) LOCO / SC inj NT	Time 2 (30min) LOCO NT / SC inj DOI	Start time (90min) LOCO DOI / (90min) LOCO / PPI	(90min) LOCO	File Name	
	5	1	20	21	286	12:26 12:46 12:48	1:18 1:20	1:41	2:02	df92d1r8	✓
	6	2	30	32	288	(134-143)	(145-159)	(161-170)	(182-191)		
	7	3	26	41	295	↓	↓	↓	↓		
	8	4	34	12	280	12:46 ↓ 1:18	↓ 1:40	2:01	2:22		
		1									
		2									
		3									
		4									
		1									
		2									
		3									
		4									
		1									
		2									
		3									
		4									
		1									
		2									
		3									
		4									
		1									
		2									
		3									
		4									
		1									
		2									

DF92 DI   NT69/DOI

☑ DOI (0.5 mg/kg)

need :

$(16 \text{ rats})\left(\dfrac{0.5 \text{ mg}}{\text{kg}}\right)\left(\dfrac{0.5 \text{ kg}}{\text{rat}}\right) = 4 \text{ mg DOI}$

weigh :

$0.00422 \text{ g} = \dfrac{4.22 \text{ mg}}{0.5 \text{ mg/ml}} = $ ☑ add : 8.44 ml saline

☑ NT69 (0.01, 0.1, 1.0 mg/kg)

need :

$(8 \text{ rats})(1.0 \text{ mg/kg})(0.5 \text{ kg/rat}) = 4 \text{ mg}$
$(8 \text{ rats})(0.1 \text{ mg/kg})(0.5 \text{ kg/rat}) = 0.4 \text{ mg}$
$(8 \text{ rats})(0.01 \text{ mg/kg})(0.5 \text{ kg/rat}) = 0.04 \text{ mg}$

need : 4.44 mg NT69

weigh :

$0.00497 \text{ g} = 4.97 \text{ mg}$

HIGH (1.0 mg/kg) $\dfrac{4.97 \text{ mg}}{1.0 \text{ mg/ml}} =$ ☑ add : 4.97 ml saline − 0.44 ml = ☑ HIGH 4.53 ml   HIGH 8 rats (at least 4 ml)

at least 0.44

MID (0.1 mg/kg)   take ☑ 0.44 ml × 9 = ☑ 3.96 ml saline
+ 0.44 ml
4.40 ml T.V. − 0.4 ml = 4.0 ml   MID 8 rats

at least 0.4 ml

LOW (0.01 mg/kg)   take ☑ 0.4 ml × 9 = ☑ 3.60 ml saline
+ 0.40 ml
☑ 4.00 ml T.V. LOW 8 rats

Experiment #: DF92 BL   **Groups:** 99 = no drug

Date: ▇▇▇▇

Session: EISOCRIT / LOCOMOTOR

Run By: KP

Comments:
Protocol # 5-062-06

Comments	1000 cage #	Box	Rat #	Group	Weight	Time 1	(60min) LOCO Time 2	(20 min) EISOCRIT Start time	File Name	
	1	1	1	99	289		1:00	2:02	df92bl r1	✓
	2	2	2		313					
	3	3	3		291					
	4	4	4	↓	290		↓2:00	↓2:22		
	5	1	5	99	277		1:24	2:26	df92bl r2	✓
	6	2	6		274					
	7	3	7		290					
	8	4	8	↓	266		↓2:24	↓2:46		
	9	1	9	99	277		1:48	2:50	df92bl r3	✓
	10	2	10		293					
	11	3	11		276					
	12	4	12	↓	277		↓2:48	↓3:10		
	1	1	13	99	282		2:12	3:14	df92bl r4	✓
	2	2	14		286					
	3	3	15		294					
	4	4	16	↓	286		↓3:12	↓3:34		
	5	1	17	99	295		2:36	3:38	df92bl r5	✓
	6	2	18		289					
	7	3	19		298					
	8	4	20	↓	284		↓3:36	↓3:58		
	9	1	21	99	300		3:00	4:02	df92bl r6	✓
	10	2	22		283					
	11	3	23		292					
	12	4	24	↓	282		↓4:00	↓4:22		
	1	1	25	99	276		3:24	4:26	df92bl r7	✓
	2	2	26		287					

Experiment #: **DF92BL** NT69/DOI Baseline   Groups: 99 = no drug

Date: ████████

Session: EISOCRIT/LOCOMOTOR

Run By: KP

Comments:

Protocol # 5-062-06

Comments	loco cage #	Box	Rat #	Group	Weight	Time 1	Time 2	Start time (LOCO 60min / EISOCRIT 20min)	File Name	
	5	1	29	99	292		3:48	4:50	df92bl r8	✓
	6	2	30		279					
	7	3	31		256					
	8	4	32		283		4:48	5:10		
	9	1	33	99	277		4:12	5:14	df92bl r9	✓
	10	2	34		276					
	11	3	35		280					
	—	4	99	99	—		5:12	5:34		
		1								
		2								
		3								
		4								
		1								
		2								
		3								
		4								
		1								
		2								
		3								
		4								
		1								
		2								
		3								
		4								
		1								
		2								

Experiment #: DF92D2

Date: ▮▮▮▮

Session: EISOCRIT/LOCOMOTOR (DF92D2)

Run By: KP

* Flip DOI Group *

Groups:	NT69	DOI
	1 = saline	1 = saline
	2 = 0.01 mg/kg	2 = 0.5 mg/kg
	3 = 0.1 mg/kg	
	4 = 1.0 mg/kg	

Comments:
Protocol # 5-062-06
Runs # 1-6 up @ 6:58 am
Runs # 7 & 8 up @ 7:07 am

Comments	loco cage #	Box	Rat #	Group	Weight	(20min) LOCO Time 1	SC inj NT Time 2	(20min) LOCO	SC inj DOI Start time	(20min) LOCO	(20min) PPI	(20min) LOCO	File Name	
	1	1	10	1 2	322	7:28	7:48	7:50	8:20	8:22	8:43	9:04	df92d2r1	✓
	2	2	12	2 1	302	(1-10)		(12-26)	(28-37)		(49-58)			
	3	3	2	3 2	354	↓		↓	↓		↓	↓		
	4	4	5	4 1	315	7:48		8:20	8:42		9:03	9:24		
	5	1	3	1 1	319	7:54	8:14	8:16	8:46	8:48	9:09	9:30	df92d2r2	✓
	6	2	8	2 2	281	(14-23)		(25-39)	(41-50)		(62-71)			
	7	3	7	3 1	318	↓		↓	↓		↓	↓		
	8	4	1	4 2	306	8:14		8:46	9:08		9:29	9:50		
PPI started 2 min late	9	1	6	4 1	295	8:20	8:40	8:42	9:12	9:14	9:35	9:56	df92d2r3	✓
	10	2	18	1 2	324	(27-36)		(38-52)	(54-63)		(75-84)			
	11	3	13	2 1	300	↓		↓	↓		↓	↓		
	12	4	4	3 2	325	8:40		9:12	9:34		9:55	10:16		
	1	1	21	4 2	322	9:28	9:48	9:50	10:20	10:22	10:43	11:04	df92d2r4	✓
	2	2	14	1 1	306	(61-70)		(72-86)	(88-97)		(109-118)			
	3	3	17	2 2	319	↓		↓	↓		↓	↓		
	4	4	9	3 1	297	9:48		10:20	10:42		11:03	11:24		
	5	1	25	3 2	298	9:54	10:14	10:16	10:46	10:48	11:09	11:30	df92d2r5	✓
	6	2	29	4 1	313	(74-83)		(85-99)	(101-110)		(122-131)			
	7	3	23	1 2	312	↓		↓	↓		↓	↓		
	8	4	22	2 1	302	10:14		10:46	11:08		11:29	11:50		
	9	1	16	3 1	309	10:20	10:40	10:42	11:12	11:14	11:35	11:56	df92d2r6	✓
	10	2	24	4 2	297	(87-96)		(98-112)	(114-123)		(135-144)			
	11	3	27	1 1	303	↓		↓	↓		↓	↓		
	12	4	19	2 2	334	10:40		11:12	11:34		11:55	12:16		
	1	1	35	2 1	304	11:28	11:48	11:50	12:20	12:22	12:43	1:04	df92d2r7	✓
	2	2	31	3 2	264	(121-130)		(132-146)	(148-157)		(169-178)			

Experiment #: DF92D2

Date: ▮▮▮▮▮

Session: EISOCRIT/LOCOMOTOR * Flip Group * DOI

Run By: KP

Comments:
Protocol #5-062-06

Groups:	NT69	DOI
	1= saline	1= saline
	2= 0.01 mg/kg	2= 0.5 mg/kg
	3= 0.1 mg/kg	
	4= 1.0 mg/kg	

Comments	Box	Rat #	Group	Weight	(20 min) LOCO Time 1	SC int NT	(20 min) LOCO Time 2	SC it DOI	(20 min) LOCO Start time	(20 min) PPI	(20 min) LOCO File Name
5	1	20	22	305	11:54	12:14	12:16	12:46	12:48	1:09	1:30 df92d2r8 ✓
6	2	30	31	302	(134-143)		(145-177)		(161-170)		(182-191)
7	3	26	42	304	↓		↓		↓	↓	↓
8	4	34	11	300	12:14	↓	12:46	↓	1:08	1:29	1:50
	1										
	2										
	3										
	4										
	1										
	2										
	3										
	4										
	1										
	2										
	3										
	4										
	1										
	2										
	3										
	4										
	1										
	2										
	3										
	4										
	1										
	2										

DF92 D2   NT69/DOI

DOI (0.5 mg/kg)

need : 4 mg DOI

weigh:
$0.004\underline{62}$ g = $\dfrac{4.62 \text{ mg}}{0.5 \text{ mg/me}}$ = ✓ add: 9.24 ml saline

NT69 (0.01, 0.1, 1.0 mg/kg)

need : 4.44 mg NT69

weigh :
$0.005\underline{00}$ g = $5.\underline{00}$ mg

HIGH (1.0 mg/kg) $\dfrac{5.00 \text{ mg}}{1.0 \text{ mg/me}}$ = ✓ add: 5.00 ml saline – 0.44 ml = ✓ 4.56 ml   HIGH 8 rats

MID (0.1 mg/kg) — take 0.44 ml × 9 = ✓ 3.96 ml saline
                                        + 0.44 ml
                                    ─────────────
                                    4.40 ml T.V. – 0.4 ml = 4.0 ml   MID 8 rats

LOW (0.01 mg/kg) — take 0.40 ml × 9 = ✓ 3.6 ml saline
                                        + 0.4 me
                                    ─────────────
                                    4.0 ml T.V   LOW 8 rats